Adjuvant treatment and outcomes for patients with stage IIIA grade 1 endometrioid endometrial cancer

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HIGHLIGHTS

- Chemotherapy is associated with improved survival for patients with stage IIIA grade 1 disease.
- Adding radiation to chemotherapy is not associated with survival benefit over chemotherapy alone.
- Lymphovascular space invasion may be predictive of worse survival.

ABSTRACT

Objective The role and type of adjuvant therapy for patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIA grade 1 endometrioid endometrial adenocarcinoma are controversial. This retrospective cohort study aimed to determine associations between adjuvant therapy use and survival among patients with stage IIIA grade 1 endometrial cancer.

Methods Patients who underwent primary surgery for stage IIIA (FIGO 2009 staging) grade 1 endometrial cancer between January 2004 and December 2016 were identified in the National Cancer Database. Demographics and receipt of adjuvant therapy were compared. Overall survival was analyzed using Kaplan–Meier curves, log-rank test, and multivariable Cox proportional hazard models.

Results Of 1120 patients, 248 (22.1%) received no adjuvant treatment, 286 (25.5%) received chemotherapy alone, 201 (18.0%) radiation alone, and 385 (34.4%) chemotherapy and radiation. Five-year overall survival rate was 83.0% (95% CI 80.1% to 85.6%). Older age, increasing comorbidity count, and lymphovascular space invasion status were significant negative predictors of survival. Over time, there was an increasing rate of chemotherapy (45.4% in 2004–2009 vs 69.2% in 2010–2016; p<0.001). In the multivariable analysis, chemotherapy was associated with significantly improved overall survival compared with no adjuvant therapy (HR 0.49 (95% CI 0.31 to 0.79); p=0.003). There was no survival association when comparing radiation alone with no treatment, and none when adding radiation to chemotherapy compared with chemotherapy alone. Those with lymphovascular space invasion (n=124/507) had improved overall survival with chemotherapy and radiation (5-year overall survival 91.2% vs 76.7% for chemotherapy alone and 27.3% for radiation alone, log-rank p<0.001), but there was no survival difference after adjusting for age and comorbidity (HR 0.25 (95% CI 0.05 to 1.41); p=0.12).

Conclusions The use of adjuvant chemotherapy for the treatment of stage IIIA grade 1 endometrial cancer increased over time and was associated with improved overall survival compared with radiation alone or chemoradiation. Patients with lymphovascular space invasion may benefit from combination therapy.

INTRODUCTION

Endometrial cancer is the fourth most common cancer in women in the USA.[1] While most patients present with early stage disease that is generally curative, those with advanced disease have a poor prognosis and optimal adjuvant therapy remains controversial.[2 3] Treatment options include chemotherapy, radiotherapy, or chemotherapy in combination with radiation. Trastuzumab may be added to chemotherapy for those with HER2neu overexpressing serous endometrial cancers.[4]

A major limitation of randomized trials on adjuvant treatment of advanced endometrial cancer is the heterogeneity of the population studied with varying stage, grade, histology, and molecular sub-type. Staging of endometrial cancer was redefined in 2009, with the change that positive cytology alone is no longer classified as stage IIIA disease. While cytology alone does not affect International Federation of Gynecology and Obstetrics (FIGO) staging, the National Comprehensive Cancer Network still recommends routine cytology collection and result reporting as positive cytology is an established adverse risk factor.[5] Among patients with advanced stage disease, those with FIGO stage IIIA grade 1 endometrioid endometrial cancer have favorable outcomes compared with those with nodal metastasis or intra-abdominal disease.[6 7] Survival rates differ based on histologic sub-type and extent of disease among patients with stage IIIA endometrial cancer, and those with low-grade endometrioid carcinomas may require a unique treatment approach.[7 8] There is a paucity of data regarding management of stage IIIA grade 1 endometrioid cancers. In two recent pivotal trials, stage

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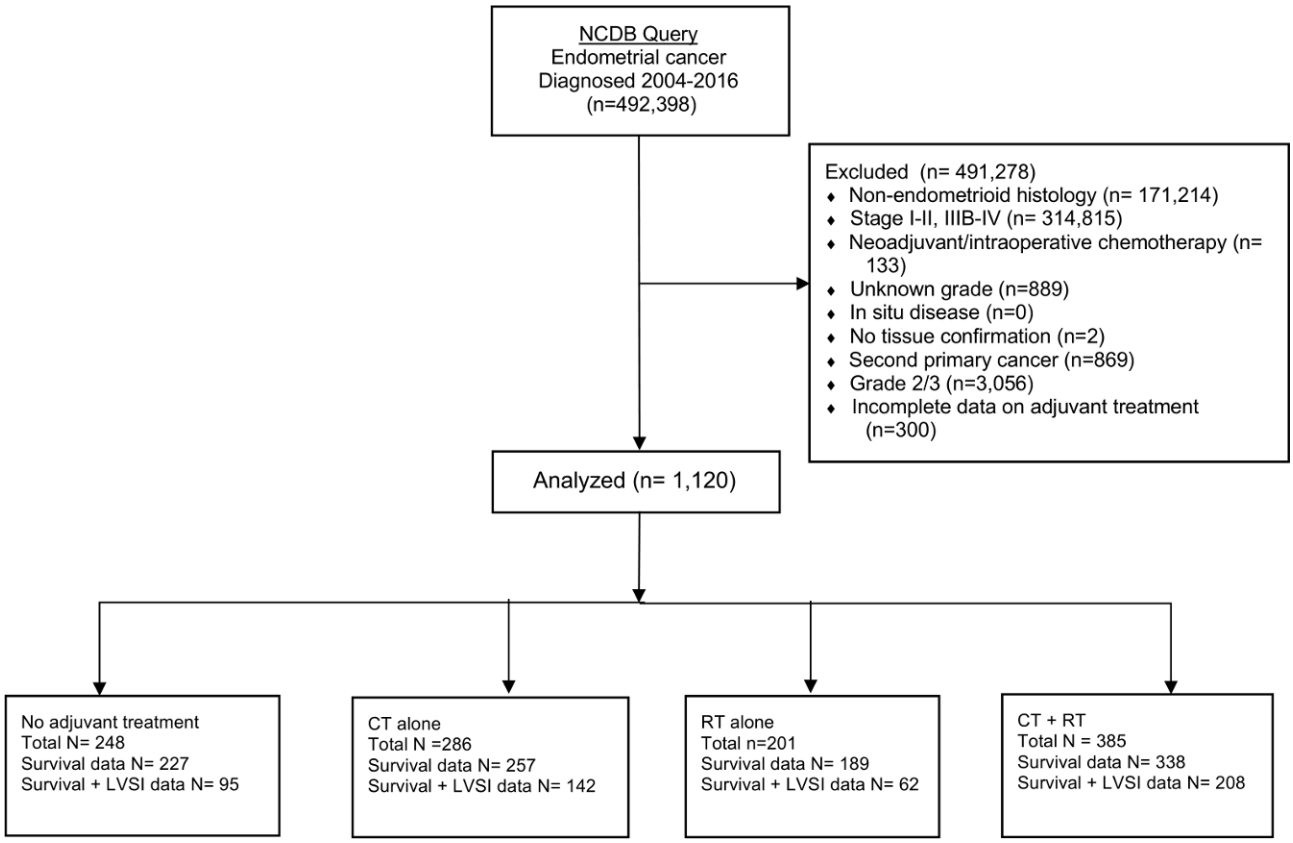

Figure 1 Identification of study cohort. CT, computed tomography; LVSI, lymphovascular space invasion; RT, radiation.

IIIA disease accounted for just 12.6% and 20.5% of patients enrolled, limiting generalizability of study results for patients in this under-represented sub-group.[9 10]

In several randomized trials comparing adjuvant radiotherapy with chemotherapy in patients with advanced stage endometrial cancer, chemotherapy was associated with improved progression-free survival and reduced risk of death.[11–13] A sub-group evaluation of those with stage IIIA disease in the GOG 122 randomized trial found that chemotherapy use was associated with improved survival.[12] The efficacy of combined adjuvant therapy versus monotherapy has been investigated in prospective clinical trials, including patients with stage IIIA disease, with mixed results. Most trials found no difference in overall survival with chemoradiation compared with monotherapy, with conflicting results regarding progression-free survival.[10 14 15] In PORTEC-3 specifically, failure-free survival was superior in the chemoradiation group compared with the radiation group, but there was no difference in overall survival between groups. Conversely, in the post-hoc survival analysis of PORTEC-3 assessing survival after recurrence and updated survival, the use of chemoradiation significantly improved overall and failure-free survival compared with radiation alone, with the greatest benefit in women with stage III disease.[9 16]

Although a prospective clinical trial on patients with stage IIIA grade 1 endometrial cancer would be ideal, it is unlikely to be feasible as this is a relatively rare sub-group of disease. Therefore, the purpose of this study was to examine treatment and outcomes for patients with stage IIIA grade 1 endometrial cancer using the National Cancer Database.

METHODS

Data Source

The National Cancer Database registry is a joint project of the American Cancer Society and Commission on Cancer of the American College of Surgeons. It contains nationwide data on oncology outcomes for over 1500 accredited programs. The database includes de-identified information on patient demographics, disease characteristics, grade, stage, treatment, and survival outcomes for nearly 70% of all newly diagnosed malignancies in the USA annually.[17]

Study Sample

A retrospective cohort study was performed from January 2004 to December 2016 on the National Cancer Database *Uterus Corpus* and *Uterus, not otherwise specified* files. We selected patients with endometrioid adenocarcinoma histology and stage IIIA (FIGO 2009 staging) disease. Site-specific coding fields (FIGO stage, pathologic tumor node metastasis stage, and tumor extension) were used to define disease stage. We excluded cases which would have been classified as stage IIIA by positive cytology alone, based on FIGO 2009 staging guidelines, patients undergoing non-standard surgical treatment, neoadjuvant/intra-operative treatment, and patients with in situ disease or lacking tissue confirmation of disease. The National Cancer Database does not code a field for adnexal tumor extension. In our effort to avoid including cases that would have been labeled as stage IIIA by positive cytology alone in older staging schemes, it is possible that some cases with adnexal involvement were excluded if they were coded as positive cytology alone. Lastly, we limited the study cohort to patients with grade 1 disease and

Table 1 Patient characteristics

Characteristic	No adjuvant treatment n=248 (22.1%)	Chemotherapy n=286 (25.5%)	Radiation n=201 (18.0%)	Chemoradiation n=385 (34.4%)	P value
Age at diagnosis (years)					<0.001
<50	50 (20.2%)	65 (22.7%)	28 (13.9%)	80 (20.8%)	
50–69	133 (53.6%)	190 (66.4%)	107 (53.2%)	274 (71.2%)	
≥70	65 (26.2%)	31 (10.8%)	66 (32.8%)	31 (8.1%)	
Race					0.52
White	223 (89.9%)	247 (86.4%)	185 (92.0%)	335 (87.0%)	
Black	11 (4.4%)	18 (6.3%)	7 (3.5%)	24 (6.2%)	
Other/multiple	14 (5.7%)	21 (7.3%)	9 (4.5%)	26 (6.8%)	
Ethnicity					0.56
Non-Hispanic/unknown	226 (91.1%)	269 (94.1%)	185 (92.0%)	352 (91.4%)	
Hispanic	22 (8.9%)	17 (5.9%)	16 (8.0%)	33 (8.6%)	
Charlson–Deyo comorbidity score					0.56
0	175 (70.6%)	213 (74.5%)	154 (76.6%)	295 (76.6%)	
1	58 (23.4%)	59 (20.6%)	37 (18.4%)	66 (17.1%)	
≥2	15 (6.1%)	14 (4.9%)	10 (5.0%)	24 (6.2%)	
Income					0.81
<$40 227	43 (17.4%)	38 (13.4%)	33 (16.5%)	51 (13.3%)	
$40 227–$50 353	62 (25.1%)	73 (25.7%)	52 (26.0%)	89 (23.2%)	
$50 354–$63 332	57 (23.1%)	71 (25.0%)	52 (26.0%)	106 (27.6%)	
≥$63 333	85 (34.4%)	102 (35.9%)	63 (31.5%)	138 (35.9%)	
Insurance					<0.001
Private	134 (54.7%)	192 (67.6%)	87 (43.9%)	258 (67.7%)	
Medicare	83 (33.9%)	53 (18.7%)	94 (47.5%)	74 (19.4%)	
Medicaid/Government other	15 (6.1%)	23 (8.1%)	10 (5.1%)	30 (7.9%)	
Uninsured	13 (5.3%)	16 (5.6%)	7 (3.5%)	19 (5.0%)	
Location					0.001
Northeast	37 (15.4%)	46 (17.2%)	47 (23.9%)	79 (21.6%)	
South	91 (37.8%)	72 (27.0%)	64 (32.5%)	90 (24.6%)	
Midwest/Central	65 (27.0%)	92 (34.5%)	60 (30.5%)	139 (38.0%)	
West	48 (29.9%)	57 (21.4%)	26 (13.2%)	58 (15.9%)	
Rurality					0.15
Metro	201 (84.5%)	232 (83.8%)	150 (78.1%)	316 (84.0%)	
Urban	36 (15.1%)	38 (13.7%)	40 (20.8%)	53 (14.1%)	
Rural	1 (0.4%)	7 (2.5%)	2 (1.0%)	7 (1.9%)	
Facility type					0.73
Non-academic	154 (62.1%)	165 (57.7%)	117 (58.2%)	232 (60.3%)	
Academic	94 (37.9%)	121 (42.3%)	84 (41.8%)	153 (39.7%)	
Distance to treatment center					0.04
<50 miles	197 (79.8%)	243 (85.6%)	175 (87.5%)	336 (87.5%)	
≥50 miles	50 (20.2%)	41 (14.4%)	25 (12.5%)	48 (12.5%)	
Year of diagnosis					<0.001
2004–2009	118 (47.6%)	101 (35.3%)	121 (60.2%)	98 (25.5%)	
2010–2016	130 (52.4%)	185 (64.7%)	80 (39.8%)	287 (74.6%)	

Continued

Table 1 Continued

Characteristic	No adjuvant treatment n=248 (22.1%)	Chemotherapy n=286 (25.5%)	Radiation n=201 (18.0%)	Chemoradiation n=385 (34.4%)	P value
Lymphovascular space invasion status					<0.001
+	27 (10.9%)	31 (10.8%)	18 (9.0%)	84 (21.8%)	
–	87 (35.1%)	136 (47.6%)	54 (26.9%)	167 (43.4%)	
Missing	134 (54.0%)	119 (41.6%)	129 (64.2%)	134 (34.8%)	
Tumor size					0.18
<2 cm	13 (5.2%)	21 (7.3%)	12 (6.0%)	21 (5.5%)	
≥2 cm	167 (67.3%)	199 (69.6%)	135 (67.2%)	290 (75.3)	
Unknown	68 (27.4%)	66 (23.1%)	54 (26.9%)	74 (19.2%)	
Lymph node dissection					0.03
No	78 (31.7%)	64 (22.4%)	58 (28.9%)	88 (22.9%)	
Yes	168 (68.3%)	222 (77.6%)	143 (71.1%)	297 (77.1%)	

excluded those with missing data on receipt of adjuvant treatment. Inclusion and exclusion criteria are summarized in Figure 1.

Study Data

Adjuvant treatment modality was categorized as none, chemotherapy alone, radiation alone, or chemoradiation (chemotherapy and vaginal brachytherapy and/or external beam radiation). Demographic information including patient age (<50, 50–69, ≥70), race (white, black, Asian/Pacific, other/unknown), ethnicity (non-Hispanic/unknown vs Hispanic), insurance status (private, Medicare, Medicaid, uninsured), Charlson–Deyo comorbidity score (0, 1, 2, ≥3), income (<$38 000, $38 000–$47 999, $48 000–$62 999, >$63 000), facility type (academic vs non-academic) and geographic region (Northeast, South, Midwest/Central, West) were collected. Clinical information included stage (IIIA), grade (1), tumor size (<2 cm, ≥2 cm, unknown), year of diagnosis (2004–2009, 2010–2016), lymph node dissection status (yes, no), and lymphovascular space invasion status (+/–/unknown). The primary outcome was overall survival in months.

Statistical Analysis

Demographics were compared by adjuvant treatment cohort using a t-test for continuous variables and χ^2 test for categorical dichotomous variables. We used Kaplan–Meier curves, log-rank test, and multivariable Cox proportional hazard models adjusting for age, comorbidity, facility type, tumor size, year of diagnosis, lymph node dissection status, and lymphovascular space invasion status to estimate overall survival based on adjuvant treatment modality. Of note, lymphovascular space invasion status was not reported prior to 2010, and tumor size was missing for approximately 25% of observations. We included unknown categories for these variables in the multivariable model to avoid excluding a significant portion of observations. We included a separate model for known lymphovascular space invasion status.

We followed STROBE guidelines for observational research. A p value <0.05 was considered significant, and all analyses were conducted with STATA V.15.1 (Statacorp, College Station, Texas, USA). This study was granted exemption by the Duke Investigational Review Board.

Table 2 Log-rank survival data

Population	5-year overall survival	P value
Radiation vs no radiation	83.8% vs 82.2%	0.45
Chemotherapy vs no chemotherapy	90.3% vs 74.0%	<0.001
Chemoradiation vs no chemoradiation	89.7% vs 79.8%	<0.001
Lymph node dissection vs no lymph node dissection	85.5% vs 75.5%	<0.001

RESULTS

A total of 1120 eligible patients were identified (Table 1); 248 (22.1%) received no adjuvant treatment, 286 (25.5%) received chemotherapy alone, 201 (18.0%) received radiation alone, and 385 (34.4%) received chemoradiation (Figure 1). The population was 88.4% white with no significant differences in receipt of adjuvant treatment by race or ethnicity. The majority of the population (74.2%) underwent a lymph node dissection. The average age was 58.3 years (range 22–90), and those who received chemotherapy were younger than those who received radiation or no adjuvant treatment (56.0 vs 61.7 years, p<0.001).

Compared with non-Medicare patients, those with Medicare were less likely to receive chemotherapy or chemoradiation but more likely to receive radiation alone. These differences were non-significant when compared with non-Medicare patients ≥65 years of age. There were no differences in receipt of adjuvant therapy based on income, high school graduate rate, rurality, or facility type. Those in the southern region were less likely to receive chemotherapy (51.1% vs 61.8%; p=0.001).

In more recent years there was a significant lower utilization of no adjuvant treatment (26.9% in 2004–2009 vs 19.1% in 2010–2016; p=0.002) and higher utilization of chemotherapy (45.4% in 2004–2009 vs 69.2% in 2010–2016; p<0.001). There was

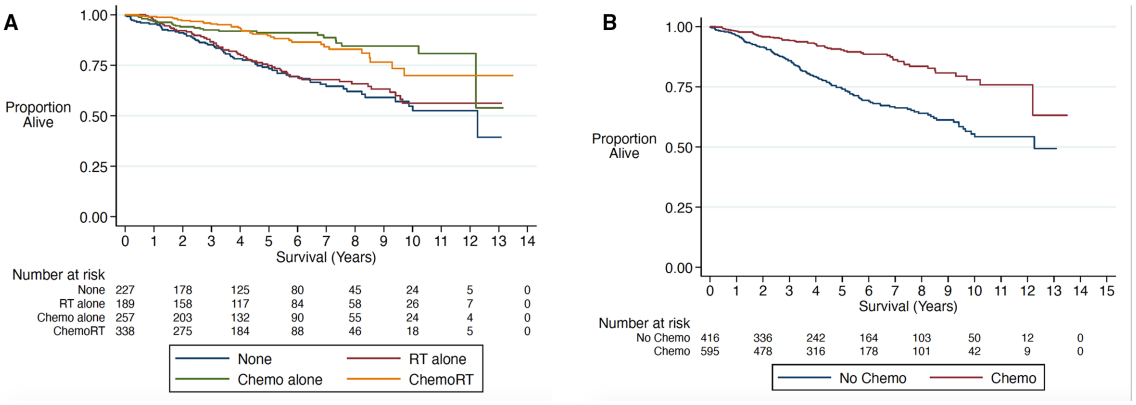

Figure 2 (A) Kaplan–Meier curves for overall survival by adjuvant treatment among women with stage IIIA, grade 1 endometrioid endometrial carcinoma in the National Cancer Database, 2004–2015. (B) Kaplan–Meier curves for overall survival by receipt of chemotherapy among women with stage IIIA, grade 1 endometrioid endometrial carcinoma in the National Cancer Database, 2004–2015.

no difference in the rate of radiation use (50.0% in 2004–2009 vs 53.8% in 2010–2016; p=0.21). There was no difference in vaginal brachytherapy or external beam radiation use. Patients with lymphovascular space invasion were more likely to receive chemoradiation than those without invasion (52.5% vs 37.6%; p=0.007).

The 5-year overall survival rate was 83.0% (95% CI 80.1% to 85.6%) (Table 2). Overall survival was significantly longer with chemotherapy versus no chemotherapy (90.3% vs 74.0%, log-rank p<0.001), and chemoradiation versus no chemoradiation (89.7% vs 79.8%, log-rank p<0.001), but there was no difference in survival with receipt of radiation (Figure 2).

In the primary multivariable Cox model, treatment with chemotherapy was associated with significantly improved overall survival compared with no adjuvant therapy (HR 0.49 (95% CI 0.31 to 0.79); p=0.003; Table 3). In contrast, there was no survival benefit from radiation alone versus no treatment, and no benefit of adding radiation to chemotherapy compared with chemotherapy alone. We assessed survival differences by radiation type independently but found no significant results. Among control variables, older age, increasing comorbidity count, and lymphovascular space invasion status were significant negative predictors of survival. Race, ethnicity, income, education level, and rurality were not associated with survival differences, and inclusion or exclusion in the multivariable model did not impact HR estimates for the characteristics included in the presented model.

Lymphovascular space invasion was a significant risk factor in the primary model (HR 2.09; p=0.006), but has only been reported since 2010. Therefore, we considered models stratified by lymphovascular space invasion status. Those without lymphovascular space invasion who received chemotherapy had a significantly better adjusted overall survival compared with no treatment (HR 0.27 (95% CI 0.09 to 0.80); p=0.019). Those with lymphovascular invasion (n=124/507) had improved unadjusted overall survival with chemoradiation compared with monotherapy by log-rank test (5-year overall survival 91.2% vs 76.7% for chemotherapy alone and 27.3% for radiation alone; p<0.001). However, after adjusting for age and comorbidity in a Cox regression model, there was no difference in overall survival with chemoradiation (HR 0.25 (95% CI 0.05 to 1.41); p=0.12) among this sub-set of patients.

DISCUSSION

Summary of Main Results

In this retrospective cohort analysis of 1120 women with stage IIIA grade 1 endometrioid adenocarcinoma from the National Cancer Database, treatment with chemotherapy was associated with significantly improved overall survival compared with no adjuvant therapy. There was no significant survival benefit from radiation alone versus no treatment, and no benefit of combined chemoradiation compared with chemotherapy alone. Our findings are similar to GOG 258 results and align with current National Comprehensive Cancer Network guidelines recommending systemic therapy with or without external beam radiation or vaginal brachytherapy for patients with stage III endometrial cancer.[5] Older age, increasing comorbidity count, and lymphovascular space invasion were statistically significant negative predictors of survival.

Results in the Context of Published Literature

Our results support the sub-group findings of prospective randomized clinical trials that have shown a survival benefit to adjuvant chemotherapy. For example, in a post-hoc subgroup analysis of GOG 122, which demonstrated an overall survival advantage for chemotherapy over radiation, patients with stage IIIA endometrioid disease were more likely to have improved overall survival with chemotherapy alone compared with those with more advanced stage disease.[12] While the Japanese Gynecologic and Oncology Group trial found no significant survival difference with chemotherapy versus radiation, a sub-group analysis that included stage IIIA disease found significantly improved survival with chemotherapy compared with pelvic radiation.[13]

Prospective clinical trials that included subjects with stage IIIA disease have also investigated the efficacy of combined adjuvant therapy compared with monotherapy, with conflicting results. In a sub-group analysis of GOG 258 by stage, including 20.5% with stage IIIA disease, no sub-stage group had relapse-free survival benefit from chemoradiation compared with chemotherapy alone.[10] A pooled analysis of the NSGO/EORTC study with the MaNGO group ILIADE-III trial containing 7.5% of subjects with stage IIIA showed improved progression-free survival but not overall survival with chemoradiation compared with radiation alone.[14] In the primary

Table 3 Multivariable logistic regression

	Overall (n=1009)		Known lymphovascular space invasion status only (n=507)	
Variable	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age				
<50	Reference		Reference	
50–69	1.89 (1.09 to 3.30)	0.02	1.22 (0.46 to 3.20)	0.69
≥70	6.70 (3.82 to 11.74)	<0.001	3.93 (1.42 to 10.9)	0.01
Adjuvant treatment				
No adjuvant treatment	Reference		Reference	
Chemotherapy only	0.49 (0.31 to 0.79)	0.003	0.49 (0.22 to 1.10)	0.08
Radiation only	0.82 (0.57 to 1.17)	0.27	0.76 (0.38 to 1.52)	0.44
Chemoradiation	1.26 (0.67 to 2.38)	0.47	0.96 (0.33 to 2.82)	0.94
Lymphovascular space invasion				
–	Reference		Reference	
+	2.09 (1.24 to 3.51)	0.006	2.44 (1.41 to 4.20)	0.001
Unknown*	0.98 (0.41 to 2.34)	0.97		
Tumor size				
<2 cm	Reference		Reference	
≥2 cm	2.22 (0.81 to 6.05)	0.12	1.46 (0.35 to 6.14)	0.60
Unknown	1.75 (0.63 to 4.89)	0.28	0.77 (0.15 to 3.94)	0.76
Lymph node dissection				
No	Reference	0.002	Reference	0.10
Yes	0.61 (0.45 to 0.84)		0.63 (0.37 to 1.09)	
Comorbidity score				
0	Reference		Reference	
1	1.15 (0.80 to 1.65)	0.45	0.74 (0.36 to 1.51)	0.41
≥2	1.66 (0.96 to 2.87)	0.07	2.61 (1.15 to 5.94)	0.02
Facility				
Non-academic	Reference		Reference	
Academic	1.08 (0.80 to 1.46)	0.61	1.13 (0.67 to 1.91)	0.65
Year of diagnosis				
2004–2009	Reference		–	
2010–2016	0.84 (0.36 to 1.96)	0.69	–	

*Lymphovascular space invasion status was not reported before 2010. Therefore, a multivariable regression model for known lymphovascular space invasion status from 2010 to 2016 is included (Online Supplemental Table 1).

multivariable sub-group analysis of PORTEC-3 there was no difference in overall survival with chemoradiation versus radiation in patients with grade 1 disease or stage III disease, but patients with stage III disease had improved failure-free survival with chemoradiation. A post-hoc analysis of PORTEC-3 suggested improved overall survival and failure-free survival with chemoradiation over radiation alone[9 16]; however, only 12.6% had stage IIIA disease and no sub-group analysis based on sub-stage has been performed. A post-hoc analysis of molecular classification of the PORTEC-3 trial showed that only patients with tumors expressing abnormal p53 protein had significantly improved recurrence-free survival with adjuvant chemoradiation compared with radiation. In further exploratory analysis, the benefit of adding chemotherapy in those with abnormal p53 expression tumors was limited to those with early stage and not demonstrated in those with stage III disease.[18] Molecular classification is being evaluated for risk stratification and adjuvant treatment in several ongoing trials.

Prior studies have examined the association between tumor grade and chemotherapy response in patients with endometrial cancer with measurable disease. McMeekin et al examined this association in four GOG endometrial cancer trials (107, 139, 167, 177) and found that, among 622 patients with endometrioid histology, there was no difference in the response to chemotherapy based on histologic grade.[19] Similarly, an analysis of primary tumor

samples from women with endometrial cancer found that grades 1–3 had similar *in vitro* responses to chemotherapy.[20] In contrast, several studies have found that grade 2 histology was associated with better response rates and improved disease-free survival compared with grade 1 or 3 histology in patients with advanced stage endometrial cancer.[21 22] While some of these retrospective studies evaluated patients with measurable disease, the conflicting nature of the results by grade further illustrates the controversy of adjuvant therapy choice. Even within our specific patient population, the percentage of patients receiving each type of therapy was fairly well distributed with 22.7% receiving no adjuvant treatment, 26.3% chemotherapy alone, 17.5% radiation alone, and 33.5% chemoradiation.

Several prior studies have used the National Cancer Database to evaluate management patterns and associations with survival in patients with stage III endometrial cancers.[23–26] Four studies found that adjuvant chemoradiation was associated with improved survival compared with monotherapy. Among these, Lester-Coll et al concluded this association was specifically in patients with stage IIIA disease, while those with grade 1 disease benefited from chemotherapy alone.[24] Syeda et al presented a sub-group analysis of women with stage IIIA tumors and found similarly decreased mortality with chemoradiation compared with chemotherapy.[25] Our study is unique from these prior studies as we focus our analysis on a specific stage, grade, and histologic sub-type of endometrial cancer together, as well as examining the use of chemotherapy, radiation, and chemoradiation.

Strengths and Weaknesses

A strength of our study is the narrow patient population with regard to histology, stage, grade, and paucity of information about this sub-group in clinical trials. This study is limited by the consequence of using a retrospective database lacking data on recurrence, treatment compliance, or complications. The National Cancer Database is hospital-based and not designed to be representative of the US population, limiting generalizability of the results.[27] The National Cancer Database does not provide comprehensive details on tumor extension type, and we were unable to compare treatment/outcomes based on extension site. The possibility of inaccuracies related to staging or lack of central pathology review is a limitation of the data.[28] In our cohort, those who received chemotherapy were younger than those who received radiation or no treatment, and those with more comorbidities were less likely to receive adjuvant treatment. The association between adjuvant treatment type, age, and comorbidity score suggest potential for bias in adjuvant therapy based on patient factors. Lymphovascular space invasion was only reported since 2010, limiting our ability to assess the association between lymphovascular space invasion status, adjuvant therapy, and survival outcomes. Thus, our results cannot provide conclusive evidence on adjuvant therapy recommendations. By excluding cases with positive cytology alone, there is a potential for error as the National Cancer Database coding is not specific to both cytology and adnexal involvement. A small number of cases with positive cytology and adnexal involvement may have been excluded. There is a lack of information regarding molecular biology, which may play a significant role in future adjuvant treatment strategy. Despite these limitations, leveraging the National Cancer Database allows for evaluation of a large sample size over time with adequate follow-up to identify associations between adjuvant treatment and survival.

Implications for Practice and Future Research

Further studies are necessary to determine which patients benefit from combined therapy. Our findings support consideration for systemic therapy, consistent with the National Comprehensive Cancer Network guidelines. While this study includes patients in the USA, further studies are needed to determine if our findings are reproducible internationally. Prospective studies are needed to determine if patients with lymphovascular space invasion benefit from additional therapy. Future trials are evaluating the clinical role of integrated clinicopathologic and molecular risk profiles to direct adjuvant treatment in patients with endometrial cancer.

CONCLUSIONS

In patients in the National Cancer Database with stage IIIA grade 1 endometrioid endometrial cancer, chemotherapy alone was associated with overall survival benefit. However, future studies are needed to identify which adjuvant treatment modality may improve survival in this specific patient population.

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Contributors MKM: guarantor, manuscript author, data compilation. BBA: NCDB search, data abstraction and compilation, statistical analysis, manuscript review and editing. AAS: manuscript review and editing. LH: manuscript review and editing. HAM: manuscript review and editing.

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